(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 March 2004 (18.03.2004)

PCT

(10) International Publication Number
WO 2004/022053 A1

(51) International Patent Classification[7]: A61K 31/40, A61P 3/06, C07D 207/34, 405/06

(21) International Application Number: PCT/IN2002/000180

(22) International Filing Date: 3 September 2002 (03.09.2002)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ATORVASTATIN CALCIUM FORM VI OR HYDRATES THEREOF

(57) Abstract: Atorvastatin calcium Form VI Or hydrates thereof, characterized by its X-ray powder diffraction and/or solid state NMR is described, as well as methods for the preparation of the same.

FIELD OF THE INVENTION

The present invention relates to Atorvastatin Calcium Form VI or hydrates thereof and a process for preparing it. Particularly the invention relates to a novel crystalline form of Atorvastatin calcium.

BACKGROUND OF THE INVENTION

Atorvastatin is a member of the class of drugs called statins. Statins drugs are currently the most therapeutically effective drugs available for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. It also appears to reduce total glycerides and total cholesterol. A high level of LDL in the blood stream has been linked to the formation of coronary lesions, which obstruct the flow of blood and can rupture and promote thrombosis. Goodman and Gilman. The *Pharmacological Basis of Therapeutics* 879 (9th ed. 1996). Reducing plasma LDL levels has been shown to reduce the risk of clinical events in patients with cardiovascular disease and patients who are free of cardiovascular disease but who have hypercholesterolemia. [Scandinavian Simvastatin Survival Study Group, 1994; Lipid Research Clinics Program, 1984a, 1984b].

The mechanism of action of statin drugs has been elucidated in some detail. They interfere with the synthesis of cholesterol and other sterols in the liver by competitively inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase enzyme ("HMG-CoA reductase"). HMG-CoA reductase catalyzes the conversion HMG-CoA to mevalonate, which is the rate determining step in the biosynthesis of cholesterol, and so, its inhibition leads to a reduction in the concentration of cholesterol in the liver. Very low density lipoprotein (VLDL) is the biological vehicle for transporting cholesterol and triglycerides from the liver to peripheral cells. VLDL is catabolized in the peripheral cells which releases fatty acids which may be stored in adipocytes or oxidized by muscle. The VLDL is converted to intermediate density lipoprotein (IDL), which is either removed by an LDL receptor, or is converted to LDL. Decreased production of cholesterol leads to an

increase in the number of LDL receptors and corresponding reduction in the production of LDL particles by metabolism of IDL.

Atorvastatin is the common chemical name of [*R-(R*, R*)*]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid. The free acid is prone to lactonization. The molecular structure of the lactone is represented by formula (I).

Atorvastatin is marketed as the hemi calcium salt-trihydrate under the name LIPITOR by Warner-Lambert Co. It is a synthetic HMG-CoA reductase inhibitor and is used for the treatment of hyperlipidemia and hypercholestorlemia. The empirical formula of Atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca$ and its molecular weight is 1155.42.

Its structural formula is :

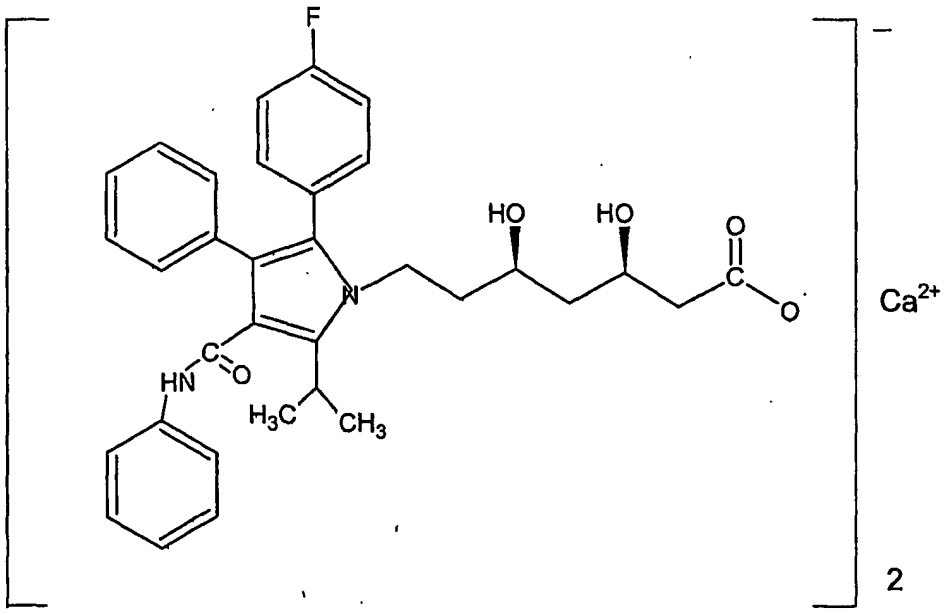


Figure : 1

Atorvastatin calcium is a white to off white amorphous or crystalline powder that is insoluble in aqueous solutions of pH 4 and below. It is very slightly soluble in distilled

water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Atorvastatin lactone was first disclosed to the public and claimed in U.S. Patent No. 4,681,893. The hemi calcium salt depicted in formula (II) (hereafter "atorvastatin calcium") an enantiomer having R- form of the ring opened acid is disclosed in U.S. Patent No. 5,273,995. This patent teaches that the calcium salt is obtained by crystallization from a brine solution resulting from the transposition of the sodium salt with $CaCl_2$ and further purified by recrystallization from a 5:3 mixture of ethyl acetate and hexane. Both of these U.S. Patents are hereby incorporated by reference.

United States Patent numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,248,,793; 5,280,132; 5,342,952; 5,007,080; 6,274,740; which are herein incorporated by reference describe various processes and key intermediates for preparing atorvastatin calcium. All these processes give mixture of crystalline and amorphous forms.

Atorvastatin is prepared as its calcium salt. The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in for administration purposes. Additionally, there is a need to produce atorvastatin in a pure and crystalline form to enable to meet exacting pharmaceutical requirements and specifications.

Furthermore, the process by which atorvastatin is produced needs to be one which is amenable to large scale production. Additionally, it is desirable that the product should be in form that is readily isolated. Finally, it is economically desirable that the product should have long shelf life without the need for specialized storage conditions.

The processes in the above United States patents disclose amorphous atorvastatin, which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen and moisture.

US Patent No. 5,969,156 discloses three polymorphs of atorvastatin designated Forms I, II, and IV by the inventors of those forms. Though the inventors claim certain processing and therapeutic advantages of their forms over the amorphous atorvastatin calcium, advantages may yet be realized by other heretofore undiscovered forms of atorvastatin calcium.

PCT application WO 97/03960 and PCT application WO 00/71116 describes method for the production of amorphous atorvastatin calcium.

PCT application WO97/03958 and US Patent No. 6,121,461 disclose the method for the preparation of Form III crystalline atorvastatin calcium while PCT application WO97/03959 teaches a method for the preparation of Form I, II, and IV of crystalline atorvastatin calcium.

PCT application WO01/36384 discloses Form V of atorvastatin calcium. All these patents claim advantages over the existing patents in one way or the other.

The present invitation includes a new crystal form of atorvastatin calcium in both hydrate and anhydrous states. Polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline or amorphous form in the solid state. A single molecule, like the atorvastatin in formula (I) or the salt complex of formula (II), may give rise to a variety of solids having distinct physical properties like solubility, stability, purity, X-ray diffraction pattern and solid state ^{13}C NMR spectrum. The differences in the physical properties of polymorphs result from the orientation and intermolecular interactions of adjacent molecules (complexes) in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula, which may be thought of as analogous to a unit cell in metallurgy, yet having distinct advantageous and/or disadvantageous physical properties compared to other forms in the polymorph family. One of the most important physical properties of pharmaceutical polymorphs is their solubility in aqueous solution, particularly their solubility in the gastric juices of a patient. For example, where absorption through the gastrointestinal

tract is slow, it is often desirable for a drug that is unstable to conditions in the patient's stomach or intestine to dissolve slowly so that it does not accumulate in a deleterious environment. On the other hand, where the effectiveness of a drug correlates with peak bloodstream levels of the drug, a property shared by statin drugs, and provided the drug is rapidly absorbed by the GI system, then a more rapidly dissolving form is likely to exhibit increased effectiveness over a comparable amount of a more slowly dissolving form.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 denotes structural formula of a new crystalline polymorphic Form VI of atorvastatin calcium of the present invention.

FIG. 2 is an X-ray powder diffractogram of atorvastatin calcium Form VI.

FIG. 3 is a solid state C^{13} NMR spectrum of atorvastatin calcium Form VI.

SUMMARY OF THE INVENTION

The present invention provides new crystalline polymorphic form of atorvastatin calcium designated as Form VI in both **anhydrous and hydrate states,** which possess the advantage of higher purity, stability and solubility.

The present invention further provides a simple cost effective process for preparing new Form VI of atorvastatin calcium that has merits of easy and rapid isolation & crystallization without comprising the purity, yield and stability. The number of steps involved is very few.

The invention also results in high yield, and very low volume of residual solvents.

Accordingly the present invention is directed to crystalline polymorphic Form VI of atorvastatin calcium **both in anhydrous and hydrate states thereof** .

The new polymorphic crystalline Form VI of atorvastatin calcium is characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 theta, d -spacings, and relative intensities with a relative intensity of > 15% measured on a Shimadzu XRD-6000 with copper K radiation of lamda 1.5406°A:

2θ	D	Relative intensity (>15%)
3.7365	23.4584	23.0
7.7200	11.4425	36.0
8.6985	10.1574	74.0
10.2185	8.6497	57.0
12.5933	7.0234	19.0
17.9103	4.9485	47.0
18.3600	4.8283	20.0
19.4031	4.5710	100.0
20.2800	4.3753	29.0
20.8200	4.2630	48.0
22.5122	3.9463	24.0
25.5848	3.4923	25.0

Further, the crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having X-ray powder diffraction peaks at 3.7, 8.6, 10.2 and 20.9 degrees at 2 theta and a broad peak at 19.5degree 2 theta.

Further the present invention is directed to crystalline Form VI atorvastatin and hydrates thereof characterized by the following solid state C^{13} nuclear magnetic

resonance spectrum (NMR) wherein chemical shift is expressed in parts per million (PPM) measured on Varian spectrophotometer:

δ(ppm)
21.898
24.294
27.767
29.368
33.939
38.275
42.836
45.980
68.932
71.266
73.617
119.357
122.987
131.214
137.515
162.696
169.066
179.540
186.890
190.640

The Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having solid state C^{13} NMR signals at about 162.689ppm, 169.066ppm, 179.54ppm, 186.89ppm, and 190.64ppm.

In a preferred embodiment of the present invention crystalline Form VI of atorvastatin calcium contains up to 8 moles of water per mole of atorvastatin calcium.

In a still preferred embodiment of the present invention crystalline Form VI of atorvastatin calcium is trihydrate.

The present invention further provides a process for the preparation of new crystalline polymorphic Form VI of atorvastatin calcium **both hydrate and anhydrous states,** [R-(R*, R*)]-2-(4-flurophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (2:1) having formula as shown in fig. 1 of the drawing accompanying this specification which comprises:

a) dissolving calcium salt of any form of atorvastatin in an **organic solvent such as** aliphatic ketone to get clear solution of atorvastatin salt,

b) optionally removing impurities,

c) adding demineralised water,

d) isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

Further the present invention also provide a process for the preparation of new polymorphic crystalline Form VI of atorvastatin calcium,[R-(R*, R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula of Fig. 1 which comprises:

a) dissolving lactone form of atorvastatin in an organic solvent preferably aliphatic ketone to get a clear solution,

b) adding an aqueous solution of alkaline solution of earth metal hydroxide and demineralised water under stirring,

c) isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

In an embodiment of the present invention, the atorvastatin calcium used may be amorphous or crystalline Form I, II, III, IV, & V of atorvastatin calcium or mixture thereof.

In a further embodiment, atorvastatin calcium used may be in anhydrous or hydrate state containing up to 9 water molecules.

In a still further embodiment an organic solvent used may be selected from aliphatic ketones having 1 to 3 carbon atoms. The aliphatic ketones used may be acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, preferably acetone.

In yet another embodiment, the organic solvent used may be 100 times preferably 15 times more preferably 10 times of the starting compound.

According to the further aspect of the invention, the dissolution may be carried out by heating the suspension of atorvastatin calcium in an organic solvent to the reflux temperature of the solvent used preferably above 40 and below 80^0C more preferably 40 to 50^0C.

In a further embodiment the impurities may be removed by filtration.

In yet another embodiment the DM water used may be 100 times preferably 10 times more preferably 5 times of the starting compound.

In another embodiment DM water may be added drop wise **maintaining the temperature** .

Further the alkaline earth metal hydroxide used may be calcium hydroxide. The aqueous solution of earth metal hydroxide may preferably be added at elevated temperature preferably above 40^0C and below 80^0C more preferably at 40 to 50^0C.

The alkaline earth metal hydroxide may be added 50 times preferably 10 times of the starting compound more preferably in 1:1ratio.

In still another embodiment the solution may be cooled slowly to a temperature in the range of –20°C to 20° (room temperature) preferably in the range of 15 to 20°C to effect crystallization. The cooling may be effected @ of 2 to 3°C.

The isolation may be effected by any conventional methods such as filtration, vacuum filtration, decantation, centrifugation.

The drying may be effected by known means like vacuum tray drier, Rotacon vacuum drier, and at a temperature above 50 and below 80°C, preferably at 55°C for 12 to 30 hours to regulate the water of molecules. One skilled in the art will appreciate that by adjusting the temperature and time for these steps one can optimize the yield of the desired product .

The new crystalline Form VI atorvastatin calcium has potential use for the treatment of hyperlipidemia, **hypercholesteromelia, hypocholesterolemia, alzheimer's disease atherosclerosis, xanthoma, and in synergism with other drugs for treatment of phytosterolemia lipase deficiency and the like.**

DETAILED DESCRIPTION OF THE INVENTION

The X-ray powder diffractogram of new polymorphic crystalline Form VI (Fig. 2) has medium peaks at 3.7 ± 0.2, 8.6 ± 0.2, 10.2 ± 0.2 and 20.9 ± 0.2 degree 2-θ and one large peak at 19.5 ± 0.2 degree 2-θ.

This X-ray pattern is well distinguished from that of known crystalline Forms I, II, III, IV, V and also from the X-ray pattern of amorphous form, which is characterised by two broad humps in the ranges 8-14 degree 2-θ and 15-26 degree 2-θ.

The X-ray powder diffractogram of FIG.2 was obtained by known methods using a Shimadzu XRD-6000, copper radiation of λ = 1.5406°A was used. Measurement range 3-40 degree 2-θ. Table 1 list the 2-θ, d-spacings and relative intensities with a relative intensity of > 15%.

TABLE- 1

2-θ	d	Relative Intensity (>15%)
3.7635	23.4584	23.0
7.7200	11.4425	36.0
8.6985	10.1574	74.0
10.2185	8.6497	57.0
12.5933	7.0234	19.0
17.9103	4.9485	47.0
18.3600	4.8283	20.0
19.4031	4.5710	100.0
20.2800	4.3753	29.0
20.8200	4.2630	48.0
22.5122	3.9463	24.0
25.5848	3.4923	25.0

The solid state C^{13} NMR spectrum of new polymorphic form is characterised by the following chemical shifts.

δ (ppm)
21.898
24.294
27.767
29.368
33.939
38.275
42.836 (strong)
45.980
68.932
71.266
73.617
119.357
122.987
131.214 (strong)
137.515
162.696
169.066169.066
179.540
186.890
190.640

The solid state C^{13} NMR spectrum is well distinguished from those of known Forms I, II, III, IV, V and also amorphous form which display a different pattern with shifts significantly different from that of new polymorphic Form VI claimed at 162.698 ppm, 169.066 ppm, 179.54, 186.89 ppm and 190.64 ppm which corresponds to C_{12} or C_{25} carbons of compound of formula of fig.1. The spectrum of fig.3 was obtained on Varian spectrometer operating at 300 MH_z. The instrument was equipped with a 13C cp mass

probe head and sample was spun at 7.0 KH_2 spin rate. The magic angle and proton decoupling efficiency were optimised before acquisition.

XRD and NMR were performed on ungrounded samples.

The new polymorphic form exits in anhydrous as well as hydrous form. It contains up to 9 water molecules. However, trihydrate form is preferable.

The invention is further illustrated by the following examples, which do not limit the effective scope of the claims.

EXAMPLE 1:

Atorvastatin Calcium (100.0 g) was added to acetone (1.0 Ltr.) at room temperature. The mixture was heated at 50°Cfor 30 minutes to get clear solution. DM-Water (500 ml) was added drop wise to this solution at 50°C. The solution was slowly cooled to room temperature at rate of 2°C/minute during which new polymorphic form of Atorvastatin Calcium crystallises out. The product is filtered by vacuum filtration and then dried in vacuum tray drier at 50-55°C for 24 hours.

Yield	:	90.0 gm (90.0%)
Relative purity (HPLC)	:	99.63%
Residual solvent	:	
Acetone	:	NMT 0.2%

EXAMPLE 2:

Atorvastatin Calcium (100.0 g) was added into acetone (100.0 ml) at room temperature. The mixture was heated at 50°Cfor 30 minutes to get clear solution. DM-Water (100 ml) was added drop wise to this solution at 50°C. The solution was slowly cooled to room temperature at rate of 2°C/minute during which new polymorphic form of Atorvastatin

Calcium crystallises out. The product is filtered by vacuum filtration and then dried in vacuum tray drier at 55-60°C for 28 hours.

	Yield	:	92.0 gm (92.0%)
	Relative purity (HPLC)	:	99.68%
	Residual solvent	:	
	Acetone	:	NMT 0.2%

EXAMPLE 3:

Atorvastatin Calcium (10.0 g) was added into acetone (1.0 Ltr.) at room temperature. The mixture was heated at 45°Cfor 20 minutes to get clear solution. DM-Water (1.0 Ltr.) was added drop wise to this solution at 45°C. The solution was slowly cooled to room temperature at rate of 2°C/minute during which new polymorphic form of Atorvastatin Calcium crystallises out. The product is filtered by vacuum filtration and then dried in vacuum tray drier at 55-60°C for 24 hours.

	Yield	:	90.0 gm (90.0%)
	Relative purity (HPLC)	:	99.61%
	Residual solvent	:	
	Acetone	:	NMT 0.2%

EXAMPLE 4:

Lactone form of Atorvastatin Calcium (100.0 g) was added into acetone (1.0 Ltr.) at room temperature. To this was added calcium hydroxide (10.0 g) suspended in DM-Water (100 ml) in one lot. The reaction mass was stirred at 45-46°C till disappearance of lactone form of Atorvastatin Calcium (TLC, 2.0 hrs.). DM-Water (400 ml) was added drop wise at 45°C. The solution was slowly cooled to room temperature at rate of 2°C/minute during which new polymorphic form of Atorvastatin Calcium crystallises out.

The product is filtered by vacuum filtration and then dried in vacuum tray drier at 50-55°C for 20 hours.

	Yield	:	100.0 gm (90.0%)
	Relative purity (HPLC)	:	99.31%
	Residual solvent	:	
	Acetone	:	NMT 0.2%

EXAMPLE 5:

Lactone form of Atorvastatin Calcium (10.0 g) was added into acetone (10.0 ml.) at room temperature. To this was added calcium hydroxide (1.0 g) suspended in DM-Water (5 ml) in one lot. The reaction mass was stirred at 50°C till disappearance of lactone form of Atorvastatin Calcium (TLC, 2.0 hrs.). DM-Water (5 ml) was added drop wise at 50°C. The solution was slowly cooled to room temperature at rate of 2°C/minute during which new polymorphic form of Atorvastatin Calcium crystallises out. The product is filtered by vacuum filtration and then dried in vacuum tray drier at 55-60°C for 24 hours.

	Yield	:	10.0 gm (90.0%)
	Relative purity (HPLC)	:	99.20%
	Residual solvent	:	
	Acetone	:	NMT 0.2%

EXAMPLE 6:

Lactone form of Atorvastatin Calcium (10.0 g) was added into acetone (1.0 Ltr.) at room temperature. To this was added calcium hydroxide (1.0 g) suspended in DM-Water (100 ml) in one lot. The reaction mass was stirred at 45-46°C till disappearance of lactone form of Atorvastatin Calcium (TLC, 2.0 hrs.). DM-Water (900 ml) was added drop wise at 45-46°C. The solution was slowly cooled to room temperature at rate of 2°C/minute

during which new polymorphic form of Atorvastatin Calcium crystallises out. The product is filtered by vacuum filtration and then dried in vacuum tray drier at 55-60°C for 24 hours.

	Yield	:	10.2 gm (92.0%)
	Relative purity (HPLC)	:	99.22%
	Residual solvent	:	
	Acetone	:	NMT 0.2%

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

CLAIMS

We Claim:

1. Atorvastatin calcium Form VI or hydrates thereof.

2. Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 theta, d -spacings, and relative intensities with a relative intensity of > 15% measured on a Shimadzu XRD-6000 with copper K radiation of lamda 1.5406°A:

2θ	D	Relative intensity (>15%)
3.7365	23.4584	23.0
7.7200	11.4425	36.0
8.6985	10.1574	74.0
10.2185	8.6497	57.0
12.5933	7.0234	19.0
17.9103	4.9485	47.0
18.3600	4.8283	20.0
19.4031	4.5710	100.0
20.2800	4.3753	29.0
20.8200	4.2630	48.0
22.5122	3.9463	24.0
25.5848	3.4923	25.0

3. Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having.

X-ray powder diffraction peaks at about 3.7, 8.6, 10.2, 18.o and 20.9 degrees at 2-θ and one large peak at 19.5 degree 2-θ.

4. Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having characterized by the following solid state C^{13} nuclear magnetic resonance spectrum (NMR) wherein chemical shift is expressed in parts per million (PPM):

δ (ppm)
21.898
24.294
27.767
29.368
33.939
38.275
42.836
45.980
68.932
71.266
73.617
119.357
122.987
131.214
137.515
162.696
169.066
179.540
186.890
190.640

5. Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having solid state C^{13} NMR signals at about 162.689ppm, 169.066ppm, 179.54ppm, 186.89ppm, and 190.64ppm.

6. Crystalline Form VI atorvastatin calcium contains up to 8 moles of water per mole of atorvastatin calcium.

7. Crystalline Form VI atorvastatin calcium is trihydrate.

8. A process for the preparation of crystalline Form VI atorvastatin calcium **both hydrate and anhydrous states,** [R-(R*, R*)]-2-(4-flurophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (2:1) having formula as shown in fig. 1 of the drawing accompanying this specification which comprises:

a) dissolving calcium salt of any form of atorvastatin in an **organic solvent such as** aliphatic ketone to get clear solution of atorvastatin salt,

b) optionally removing impurities,

c) adding demineralised water,

d) isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

9. A process for the preparation of new polymorphic crystalline Form VI of atorvastatin calcium,[R-(R*, R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula of Fig. 1 which comprises:

a. dissolving lactone form of atorvastatin in an organic solvent preferably aliphatic ketone to get a clear solution,

b. adding an aqueous solution of alkaline solution of earth metal hydroxide and demineralised water under stirring,

c. isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

10. A process of claim 8 wherein the atorvastatin calcium used is amorphous or crystalline Form I, II, III, IV, & V of atorvastatin calcium or mixture thereof.

11. A process of claim 8 wherein the atorvastatin calcium used is in anhydrous or hydrate state containing up to 9 water molecules.

12. A process of claim 8 wherein an organic solvent used is selected from aliphatic ketones having 1 to 3 carbon atoms.

13. A process of claim 8 and 10 wherein the aliphatic ketones used are acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, preferably acetone.

14. A process of claim 8 wherein the organic solvent used is 100 times preferably 15 times more preferably 10 times of the starting compound.

15. A process of claim 8 wherein the dissolution is carried out by heating the suspension of atorvastatin calcium in an organic solvent to the reflux temperature of the solvent used preferably above 40 and below 80^0C more preferably 40 to 50^0C.

16. A process of claim 8 wherein the impurities are removed by filteration.

17. A process of claim 8 wherein the demineralised (DM) water used is 100 times preferably 10 times more preferably 5 times of the starting compound.

18. A process of claim 8 wherein DM water is added drop wise **maintaining the temperature** .

19. A process of claim 9 wherein the alkaline earth metal hydroxide used is calcium hydroxide.

20. A process of claim 9 wherein the aqueous solution of earth metal hydroxide is preferably added at elevated temperature preferably above 40^0C and below 80^0C more preferably at 40 to 50^0C.

21. A process of claim 9 wherein the alkaline earth metal hydroxide added is 50 times preferably 10 times of the starting compound more preferably in 1:1ratio.

22. A process of claims 8 & 9 wherein the cooling is effected slowly to a temperature in the range of –20°C to 20° (room temperature) preferably in the range of 15 to 20°C to effect crystallization. The cooling may be effected @ of 2 to 3°C.

23. A process of claims 8 & 9 wherein the isolation is carried out by conventional methods such as filtration, vacuum filtration, decantation, centrifugation.

24. A process of claims 8 & 9 wherein the drying is effected by known means like vacuum tray drier, rotacon vacuum drier, and at a temperature above 50 and below 80^0C, preferably at 55^0C for 12 to 30 hours.

AMENDED CLAIMS

[received by the International Bureau on 08 May 2003 (08.05.03);
original claims 1 to 24 replaced by amended claims 1 to 22; (5 pages)]

1. A **crystalline** Form VI atorvastatin calcium or hydrates thereof **having characterized by the X-ray powder diffraction pattern following 2 θ values measured using a Shimadzu XRD-6000 with copper K radiation of λ1.5406°A and with a relative intensity of > 15%**
3.7365, 7.7200, 8.6985, 10.2185, 12.5933, 17.9103, 18.3600, 19.4031, 20.2800, 20.8200, 22.5122, and 25.5848

2. A crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having X-ray powder diffraction peaks at about 3.7, 18.0, and 20.9 degrees at 2-θ and **large** peaks at **8.6, 10.2,** and 19.5 degree 2-θ.

3. A crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having characterized by the following solid state C^{13} nuclear magnetic resonance spectrum (NMR) wherein chemical shift is expressed in parts per million (PPM):

δ (ppm)
21.898
24.294
27.767
29.368
33.939
38.275
42.836

45.980
68.932
71.266
73.617
119.357
122.987
131.214
137.515
162.696
169.066
179.540
186.890
190.640

4. A crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having solid state C^{13} NMR signals at about 162.689ppm, 169.066ppm, 179.54ppm, 186.89ppm, and 190.64ppm.

5. A crystalline Form VI atorvastatin calcium of claim 1 contains up to 8 moles of water per mole of atorvastatin calcium.

6. A crystalline Form VI atorvastatin calcium of claim 1 contains up to 3 moles of water per mole of atorvastatin calcium.

7. **A crystalline Form VI atorvastatin calcium of claim 1 has melting point in the range of 177 to 182^{o}C**

8. A process for the preparation of a crystalline Form VI atorvastatin calcium of claim 1 both hydrate and anhydrous states, [R-(R*, R*)]-2-(4-flurophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (2:1) having formula as shown in fig. 1 of the drawing accompanying this specification which comprises:

a) dissolving calcium salt of any form of atorvastatin in an organic solvent such as aliphatic ketone **preferably at a temperature in the range of ambient to reflux temperature** to get clear solution of atorvastatin salt,

b) optionally removing impurities,

a) adding demineralised water **maintaining the same temperature,**

d) isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

9. A process for the preparation of new polymorphic crystalline Form VI of atorvastatin calcium,[R-(R*, R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula of Fig. 1 which comprises:

a) dissolving lactone form of atorvastatin in an organic solvent preferably aliphatic ketone **at a temperature in the range of ambient to reflux temperature** to get a clear solution,

b) adding an aqueous solution of alkaline solution of earth metal hydroxide and demineralised water under stirring **maintaining the same temperature,**

c) isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

10. A process of claims 8 & 9 wherein the atorvastatin calcium used is amorphous or crystalline Form I, II, III, IV, & V of atorvastatin calcium or mixture thereof.

11. A process of claims 8 & 9 wherein the atorvastatin calcium used is in anhydrous or hydrate state containing up to 9 water molecules.

12.A process of claims 8 & 9 wherein an organic solvent used is selected from aliphatic ketones having 1 to 3 carbon atoms.

13.A process of claims 8, 9 and 12 wherein the aliphatic ketones used are acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, preferably acetone.

14.A process of claims 8 & 9 wherein the organic solvent used is 100 times preferably 15 times more preferably 10 times of the starting compound.

15.A process of claims 8 & 9 wherein the dissolution is carried out by heating the suspension of atorvastatin calcium in an organic solvent to above 40 and below 80^{0}C more preferably 40 to 50^{0}C.

16.A process of claims 8 & 9wherein the impurities are removed by filtration.

17.A process of claims 8 & 9 wherein the demineralised (DM) water used is 100 times preferably 10 times more preferably 5 times of the starting compound.

18.A process of claim 9 wherein the alkaline earth metal hydroxide used is calcium hydroxide.

19.A process of claim 9 wherein the alkaline earth metal hydroxide added is 50 times preferably 10 times of the starting compound more preferably in 1:1ratio.

20.A process of claims 8 & 9 wherein the cooling is effected slowly to a temperature in the range of –20°C to 20° (room temperature) preferably in the range of 15 to 20°C to effect crystallization. The cooling may be effected @ of 2 to 3°C.

21.A process of claims 8 & 9 wherein the isolation is carried out conventional methods such as filtration, vacuum filtration, decantation, centrifugation.

22.A process of claims 8 & 9 wherein the drying is effected by known means like vacuum tray drier, rotacon vacuum drier, and at a temperature above 50 and below 80^0C, preferably at 55^0C for 12 to 30 hours.

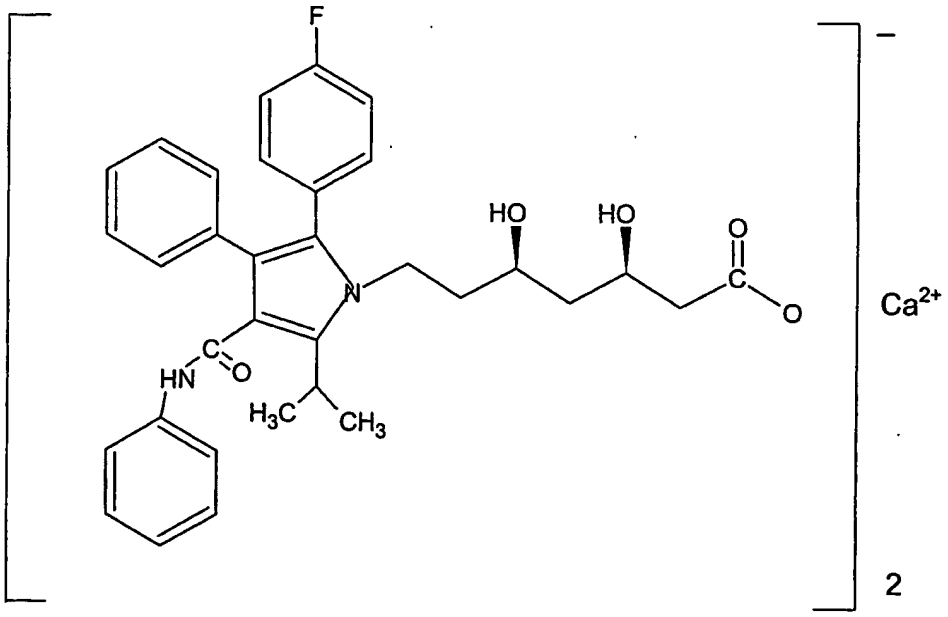
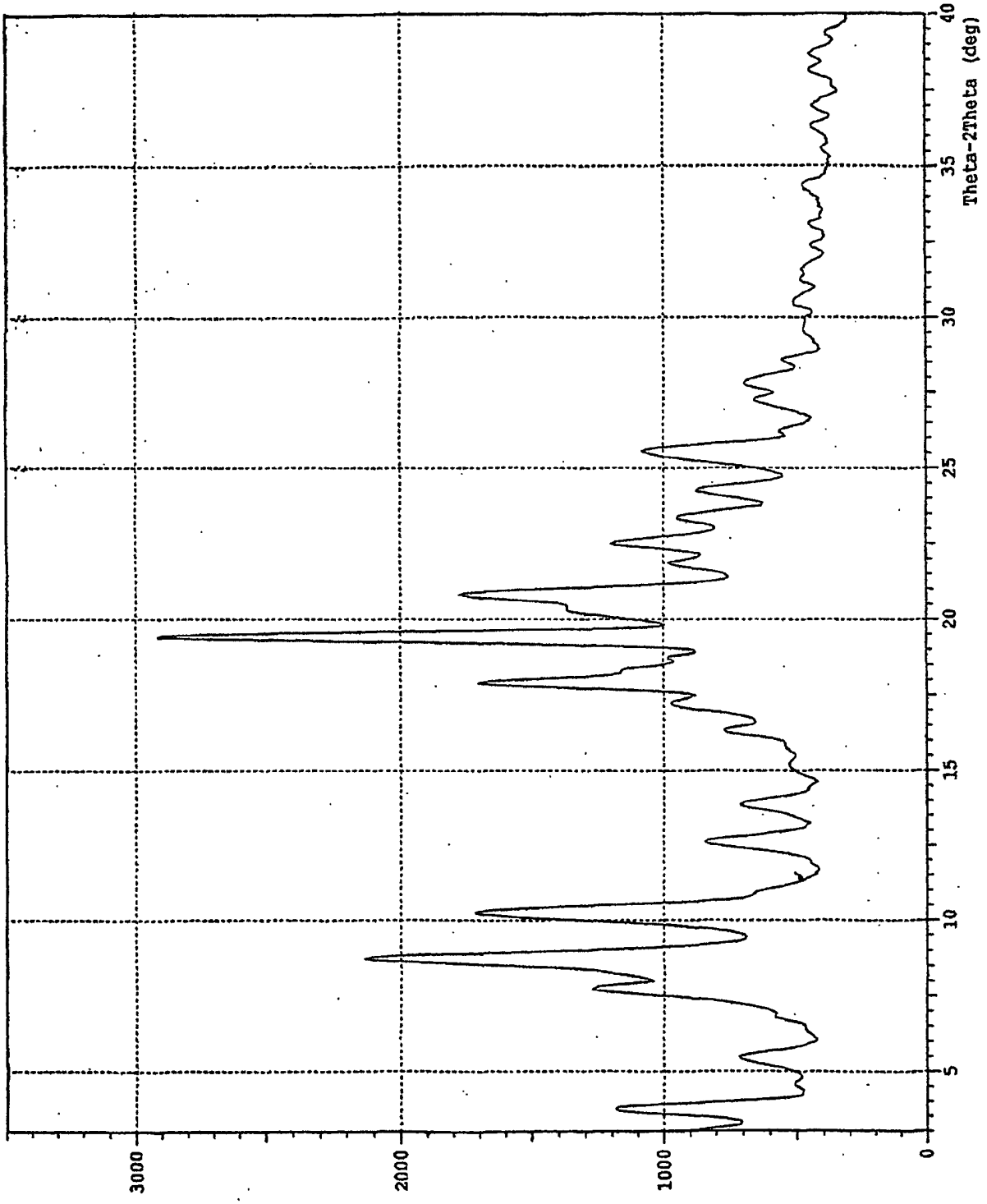


Figure : 1


Theta-2Theta (deg)
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20
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30
35
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1000
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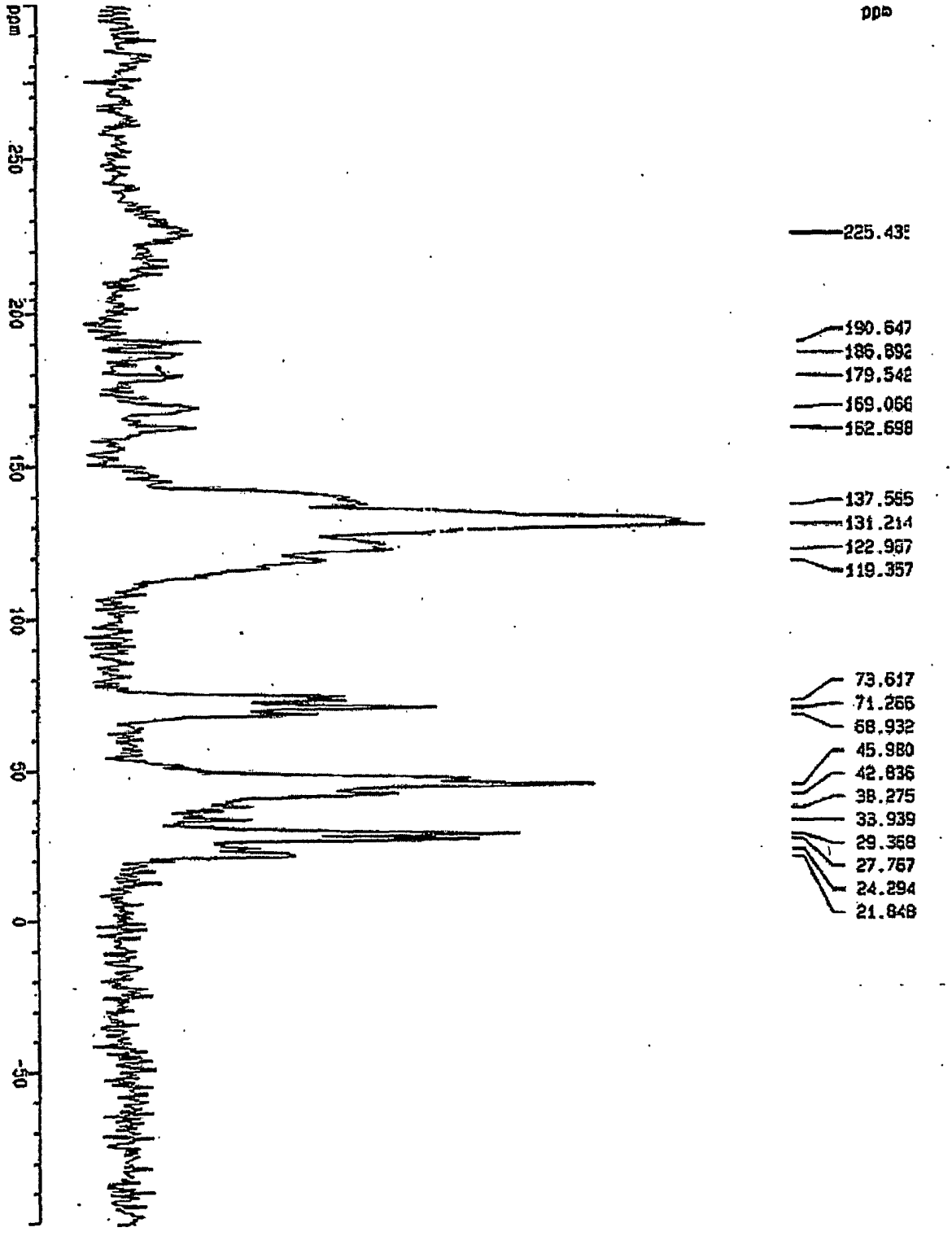
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179.542
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131.214
122.967
119.357
73.617
71.266
68.932
45.980
42.836
38.275
33.939
29.368
27.767
24.294
21.848

INTERNATIONAL SEARCH REPORT

tn tional Application No
PCT/IN 02/00180

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/40 A61P3/06 C07D207/34 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 43732 A (ISHAI ETI ;SAMBURSKY GUY (IL); TEVA PHARMA (IL); ARONHIME JUDITH () 6 June 2002 (2002-06-06) page 6, line 19 - line 27; claims 1-3,7; figure 1; example 1	1-8, 10-18, 22-24
E	WO 03 004470 A (BYRN STEPHEN ROBERT ;COATES DAVID ANDREW (US); KRZYZANIAK JOSEPH F) 16 January 2003 (2003-01-16) Form VII page 54, line 10 - line 29; figures 3,27	1-8, 10-18, 22-24
X	WO 02 051804 A (SCHOENING KAI-UWE ;SZELAGIEWICZ MARTIN (CH); VAN DER SCHAAF PAUL A) 4 July 2002 (2002-07-04) claim 15; example 8B	9,19-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2003	12/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/IN 02/00180

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1 (part), 6 (part), 7 (part), 9 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 (part), 6 (part), 7 (part), 9 (part)

Claim 1 discloses an atorvastatin calcium salt designated Form VI. No further data is given to enable the skilled man to ascertain whether a particular crystalline form of atorvastatin calcium salt falls within the scope of this claim. The same is true for claims 6 and 7, in which the only further data is the amount of water contained by the crystals. The search has therefore been performed for the subject matter of claim 1 which has the parameters given in one of claims 2-5, or which has been prepared according to the processes of claims 8 or 9.
It appears that the process of claim 9 could only lead to the calcium salt product if the metal hydroxide used is calcium hydroxide. The search has been made on this basis.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/IN 02/00180

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0243732 A	06-06-2002	AU 1792702 A	11-06-2002
		WO 0243732 A1	06-06-2002
		US 2002183378 A1	05-12-2002
		AU 3289102 A	11-06-2002
		WO 0243667 A2	06-06-2002
		US 2002099224 A1	25-07-2002
WO 03004470 A	16-01-2003	WO 03004470 A1	16-01-2003
WO 02051804 A	04-07-2002	WO 02051804 A1	04-07-2002